Chemical Composition and Biological Potential of *Cedrus atlantica* Essential Oil Assessed through In Vitro and In Silico Approaches

Abstract

Cedrus atlantica (L.) is a medicinal plant traditionally used by indigenous populations to treat various ailments. This study aimed to extract the essential oil of *C. atlantica* (EO-CA), characterize its chemical profile, and evaluate its in vitro biological activities. Phytochemical characterization was performed using GC-MS, while antioxidant potential was assessed using the DPPH, FRAP, and TAC methods. Antimicrobial activity was evaluated on solid media. GC-MS analysis revealed a rich phytochemical composition, with 99.98% of the essential oil components identified. A total of 32 compounds were detected, with linalool (26%) and borneol (12%) being the most abundant. Antioxidant activity evaluation yielded promising results, with an IC_{50} of 48.52 ± 3.26 µg/mL in the DPPH assay, an EC_{50} of 415.62 ± 13.60 µg/mL in the FRAP assay, and a total antioxidant capacity of 865.0 ± 14.14 µg AAE/mg in the TAC assay. Regarding antimicrobial activity, EO-CA exhibited inhibition zones ranging from 19.65 mm to 25.45 mm, with the largest zone observed against *Klebsiella pneumoniae*. Antifungal evaluation also demonstrated positive results, with inhibition zones ranging from 19.69 mm to 23.83 mm, with *Candida albicans* showing the strongest inhibition. *In silico* analysis identified sabinene hydrate as the most potent inhibitor of NADPH oxidase, with a docking score of -5.817 kcal/mol, followed by cryptone (-5.656 kcal/mol) and carvacrol (-5.548 kcal/mol). These findings indicate that *C. atlantica* essential oil is rich in bioactive compounds, conferring notable biological and pharmacological properties. The results support the traditional use of this plant and suggest its potential as a promising source of novel natural therapeutic agents.

Key words: *Cedrus*; Plant; Phytochemical ; DPPH; GC-MS; Antimicrobial

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Abbreviations

EO-CA: Essential oil of *C. atlantica* ; **DPPH** : 2,2-diphenyl-1-picrylhydrazyl radical ; **GC-MS** : Gas chromatography-mass spectrometry ; **TAC** : Total Antioxidant Capacity ; **BHT** : Butylated hydroxytoluene ; **TCA** : Trichloroacetic acid ; **FRAP** : Ferric reducing antioxidant power ; **TTC** : 2,3,5-triphenyltetrazolium chloride ; Flu : Fluconazole ; Amp : ampicillin.

1. Introduction

Herbal medicine, one of the oldest forms of medicine practised by mankind, is still widely used around the world today [1,2]. Medicinal plants are particularly sought after for their high therapeutic potential and low toxicity [3–5]. According to the World Health Organization (WHO), more than 80% of the world's population relies on traditional medicine to meet their primary healthcare needs [6,7]. In addition, 74% of plant medicines used in modern medicine are directly related to their traditional use [8,9].

The presence of physiologically active phenolic compounds is a major factor supporting the assumed therapeutic effectiveness of many medicinal plants. According to Tavares et al. (2013) [10], these substances are known for their numerous positive properties, which include anti inflammatory, antioxidant, insulin-regulating, anticarcinogenic, antiviral, antiulcer, antiapoptotic, neuroprotective, and cardioprotective.

Oxygen-dependent stress, which arises from free radical generation, is widely acknowledged as one of the primary causes of various diseases, including diabetes, cancer, hypertension, and Alzheimer's disease. In response to these threats, scientists and nutritionists are working to identify natural compounds with antioxidant properties to lessen oxidative damage [11] and to replace synthetic antioxidants, such as those that have been declared carcinogenic [12].

Essential oil (EOs) are complex mixtures of chemical compounds belonging to various families, including aldehydes, alcohols, esters, phenols, ethers, ketones, terpenes, and others. Their chemical composition has been extensively studied, revealing a wide variety of potentially bioactive molecules that confer multiple biological and pharmacological effects. Among these components, terpenes, terpenoids, and other aromatic or aliphatic compounds of low molecular weight predominate, contributing significantly to their biological properties [13–15].

The medical community faces ongoing challenges from the advent of novel diseases, the rise of antibiotic-resistant pathogenic bacteria [16], and gastrointestinal issues related to anti-inflammatory drug use [17].

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Cedrus atlantica, a species endemic to the North African Middle Atlas, belongs to the *Cedrus* genus and the Pinaceae family [18]. The essential oils derived from this species are extensively utilized in the production of various products, including perfumes and certain hygiene items [18,19]. As highlighted in the literature, the chemical composition of *C. atlantica* essential oils encompasses a diverse array of bioactive compounds, classified into different groups such as oxygenated sesquiterpenes and sesquiterpene hydrocarbons [18]. The qualitative and quantitative profiles of these phytochemical compounds, however, are influenced by several intrinsic and extrinsic factors, including the plant's geographical origin, harvesting season, soil composition (Zn, Fe, Cu), climatic conditions, and the applied extraction and processing methods [18,20].

This study aims to evaluate the biological properties of essential oil extracted from the leaves of *Cedrus atlantica* (L.). The objective is to assess their antioxidant potential *in vitro* using complementary methods (DPPH, FRAP, TAC), their antimicrobial activity against bacterial and fungal strains, and their molecular interactions through *in silico* evaluation, to better understand their mechanisms of action and therapeutic potential.

2. Material and method

2.1. Reagents and Chemicals

Reagents and chemicals used in this study include ammonium molybdate ($(NH_4)_6Mo_7O_{24}$), sodium phosphate, butylated hydroxytoluene (BHT), 2,2-diphenyl-1-picrylhydrazyl radical (DPPH), quercetin, ascorbic acid, gallic acid, potassium ferricyanide ($K_3[Fe(CN)_6]$), ferric chloride ($FeCl_3$), resazurin, agar, fluconazole, trichloroacetic acid (TCA) and 2,3,5-triphenyltetrazolium chloride (TTC). All these products were purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.2. Plant material and identification of the plant

This medicinal plant was collected between March and April 2023 in a mountainous region (33.432778, -5.175914) and identified by a botanist. A reference sample has been deposited with the Biology Department under registration number CA/ifr/23. *C. atlantica* leaves were dried under cover at a temperature of around 40°C for three days. The dried leaves were then ground using an electric mixer to obtain a powder for extraction of the plant's essential oil [21].

2.3. Isolation and extraction of *C. atlantica* essential oil

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Using a Clevenger apparatus, 100 grams of *C. atlantica* leaf powder were mixed with 750 mL of distilled water, then placed in a 1000 mL heating flask. The extraction temperature was gradually increased until the boiling point was reached, at around 100°C. The essential oil were separated due to the difference in density, with the *C. atlantica* essential oil (EO-CA) accumulating above the aqueous phase. The essential oil obtained were isolated and stored in amber bottles at a temperature of around 4°C, with a view to phytochemical characterisation and evaluation of the biological activities of EO-CA [22].

2.4. Identification of phytochemical compounds in EO-CA

In this study, GC-MS was used to accurately analyse and identify the various phytocompounds present in *C. atlantica* essential oil. The analysis was carried out using a gas chromatograph (GC) model Agilent Technologies 6890 N Network (Little Falls, California, USA) equipped with an HP-5MS capillary column (dimensions: 30.00 m × 0.250 mm × 0.250 µm film thickness). The flame ionisation detector (FID) was set at a temperature of 260.0°C. A volume of 1.00 µL of sample was injected in split mode at 250.0°C. During the chromatographic process, helium was used as the carrier gas at a constant flow rate of 1.00 mL/min. The column temperature was programmed to increase progressively by 0.5°C/min, starting at 35°C and reaching 250.0°C. Essential oil components were identified using Kovats retention indices, compared to a set of n-alkane homologues. In addition, the NIST MS Library (v. 2.0) was used to refine compound identification [23,24].

2.5. Antioxidant power

2.5.1. DPPH test

To assess the antioxidant activity of *C. atlantica* essential oil (EO-CA), 25 µL of each methanolic solution of EO-CA, prepared at different concentrations, was mixed with 975 µL of methanolic solution of DPPH (2.4 mg/100 mL methanol). A negative control was obtained by mixing 25 µL of methanol with 975 µL of DPPH solution in methanol. After rapid mixing by vortexing, the samples were incubated at room temperature, protected from light, for 30 minutes. The absorbance of the solutions was then measured at 517 nm. The results are expressed either as free radical scavenging activity or as percentage free radical inhibition (Inh%) calculated using the following formula [25]:

$$Inh\ (\%) = \left[1 - \frac{OD\ samp}{OD\ cont}\right] * 100 \qquad (1)$$

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Where Inh (%) represents the percentage of anti-free radical activity; ODsamp refers to the absorbance of the sample after 30 minutes; and ODcont refers to the absorbance of the negative control after 30 minutes.

2.5.2. FRAP test

To evaluate the reducing power of EO-CA, we applied the method described by Oyaizu [26]. Volumes of 1 mL of EO-CA solutions at various concentrations were placed in tubes, to which were added 2.5 mL of 0.2 M phosphate buffer (pH 6.6) and 2.5 mL of 1% potassium ferricyanide $K_3Fe(CN)_6$ solution. The mixtures were incubated at 50°C for 20 minutes. After this step, 2.5 mL of 10% trichloroacetic acid was incorporated to stop the reaction. Next, 2.5 mL of this mixture was combined with 2.5 mL of distilled water and 0.5 mL of a 0.1% $FeCl_3$ solution prepared just prior to analysis. The absorbance of the reaction medium was measured at a wavelength of 700 nm.

2.5.3. TAC test

For this evaluation, 1 mL of reagent solution (composed of 0.6 M sulphuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate) was mixed with 25 µL of EO-CA. The mixture was incubated at 95°C for 90 minutes. After this incubation, the optical density was measured at 695 nm using a spectrophotometer, with a reference blank prepared using 25 µL methanol instead of EO-CA. Antioxidant capacity was expressed in milligrams of ascorbic acid equivalent per gram of extract (µg EAA/mg), based on a standard ascorbic acid curve [27].

2.6. Antimicrobial Activity of EO-CA

2.6.1. Microbial Strains

The antimicrobial activity of EO-CA was evaluated against three fungal strains (*Candida albicans*, *Saccharomyces cerevisiae* and *Aspergillus niger*) and three bacterial strains (*Staphylococcus aureus*; *Escherichia coli* and *Klebsiella pneumoniae*), which were obtained by Sidi Mohammed Ben Abdellah University (Fez, Morocco).

2.6.2. Antibacterial activity

The antibacterial activity of OE-CA was determined using the disk diffusion method [28]. Petri dishes containing Mueller-Hinton were inoculated with the three bacterial strains using the double-layer method. From fresh cultures grown in Mueller-Hinton media, serial dilutions were made in sterilized saline (NaCl, 0.9%) to a turbidity of 0.5 McFarland (10^6-10^8 CFU/mL). Then, 100 µL of each strain were added to tubes containing 5mL of soft agar (0.5% agar), and the inoculated tubes were seeded into Petri dishes containing Mueller-Hinton media. Whatman No.

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4 paper discs, 6 mm in diameter, were impregnated with 20 µL of EO-CA. Plates were incubated at 37°C. Diameters and percentage of inhibition were measured after 24 h. A negative control and a positive control containing ampicillin for bacterial strains were carried out in the same way as the other tests.

2.6.3. Antifungal activity

To assess the antifungal activity of EO-CA against *Candida albicans*, *Saccharomyces cerevisiae* and *Aspergillus niger.* The direct confrontation method in malt extract medium between EO-CA was used [29,30]. Briefly, Whatman No. 4 paper discs with a diameter of 6 mm were impregnated with 20 µL of EO-CA, and a 6 mm disc of agar containing the fungal strain was placed 1 cm from the disc containing EO-CA. Plates were incubated at 27°C. Diameters and percentage of inhibition were measured after 48 h. A negative control and a positive control containing fluconazole for fungal strains were carried out in the same way as the other tests.

2.6.4. Determination of Minimum Inhibitory Concentration (MIC)

The broth dilution method was employed to evaluate the antimicrobial activity. Serial dilutions of EO-CA were prepared in a 96-well microplate. Each well contained culture medium, an adjusted inoculum (10^6 CFU/mL for bacteria, 10^4 spores/mL for fungi), and essential oil dilutions. The MIC was determined by visually observing microbial growth in the wells or via colorimetric assessment using 0.2% TTC (w/v). After incubation at 37°C for 24 hours (bacteria) or 48 hours (fungi), the MIC was identified as the lowest concentration with no visible turbidity [22,31].

2.7. Molecular Docking

Molecular docking was employed to theoretically investigate the antioxidant and antimicrobial potential of essential oil (EO) components extracted from *Cedrus atlantica* (L.). The selection of target proteins was based on their roles in key biological processes such as oxidative stress, microbial virulence, and survival. NADPH oxidase (2CDU), involved in the production of reactive oxygen species, was chosen to evaluate the antioxidant activity of the compounds. Beta-ketoacyl-[acyl carrier protein] synthase (1FJ4) and nucleoside diphosphate kinase (3Q8U), which play critical roles in fatty acid biosynthesis and bacterial energy metabolism, were selected to assess antibacterial properties. Finally, beta-1,4-endoglucanase (5I77) and sterol 14-alpha demethylase (CYP51, 5FSA), crucial for the growth of pathogenic fungi, were included to analyze the antifungal effects of the EO compounds. This methodological approach

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ensures a comprehensive exploration of the biological activities of the identified bioactive compounds.

2.7.1. Ligand Preparation

Ligand preparation began by obtaining the EO constituents of *Cedrus atlantica (L.)* from the PubChem database in SDF format. The LigPrep module from Schrödinger software (version 11.5) was used to prepare these ligands using the OPLS3 force field. Each molecule underwent ionization state optimization at pH 7.0 ± 2.0, generating up to 32 possible stereoisomers for each compound [32,33].

2.7.2. Protein Preparation

Proteins used for docking were retrieved from the Protein Data Bank, including structures of human NADPH oxidase (PDB ID: 2CDU), *E. coli* beta-ketoacyl-[acyl carrier protein] synthase (PDB ID: 1FJ4), *S. aureus* nucleoside diphosphate kinase (PDB ID: 3Q8U), *A. niger* beta-1,4-endoglucanase (PDB ID: 5I77), and sterol 14-alpha demethylase (CYP51) from *C. albicans* (PDB ID: 5FSA). The protein preparation process involved refining the structures by adding hydrogen atoms, correcting bond orders, removing water molecules, assigning hydrogen bonds, optimizing receptor atom charges, and minimizing energy using the OPLS3 force field [34,35].

2.7.3. Glide Standard Precision (SP) Ligand Docking

Flexible ligand docking was performed using the SP (Standard Precision) mode in Glide from Schrödinger-Maestro version 11.5. Non-cis/trans amide bonds were penalized during the docking process. For the ligand atoms, Van der Waals interactions were scaled with a factor of 0.80, and the partial charge cutoff was set to 0.15. The docking results were evaluated based on the glide score, which was derived from the energy-minimized poses of the ligands. The pose with the lowest glide score for each ligand was selected as the best docking result [36,37].

2.8. Statistical analysis

Experimental results were presented as mean ± standard deviation. Statistical analysis was performed using GraphPad Prism software (version 8). Statistical differences between groups were assessed using a one-way analysis of variance (ANOVA), followed by Tukey's test for multiple comparisons. A threshold of statistical significance was set at $p<0.05$ for all analyses.

3. Results and discussion

3.1. Phytochemical identification of EO-CA

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C. atlantica essential oil was extracted with a notable yield of 11%, indicating a significant concentration of volatile compounds. GC-MS analysis revealed a rich and diverse chemical composition, dominated by linalool (26.86%) (Table 1 and Figure 1), a compound known for its calming, antibacterial and anti-inflammatory properties [38]. Borneol (12.47%) and eucalyptol (9.85%) are also present in significant quantities, reinforcing the therapeutic potential of this oil for applications in the treatment of inflammation and respiratory infections [39]. Other compounds, such as alpha-bisabolene (5.30%) and elemol (6.08%), contribute to the oil's complexity and efficacy, offering anti-inflammatory and antioxidant properties [40–42]. The repartition of compounds shows a predominance of monoterpenes at 67.08%, followed by sesquiterpenes representing 25.52%, while other compounds make up 7.83% (Table 1 end Figure 1).

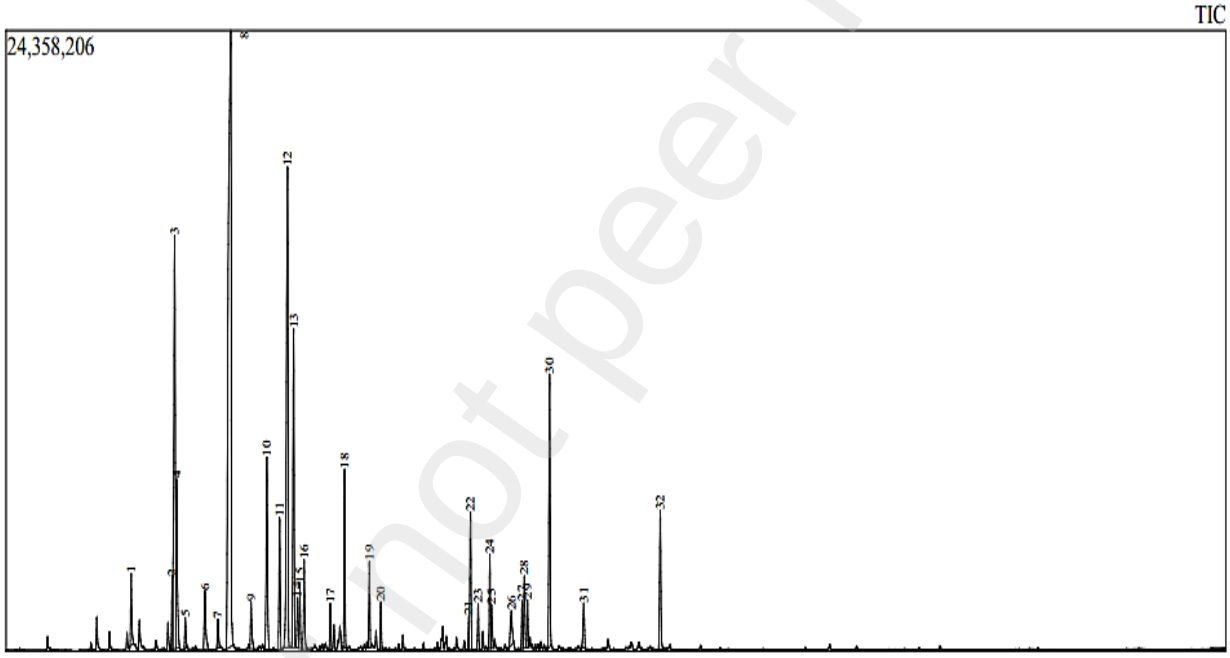

Figure 1. Chromatographic profile of *C. atlantica* essential oil (EO-CA)

Table 1. Phytochemical identification of volatile compounds extracted from *C. atlantica*

Peak	Name	Cl. CH	CH. Fo	Rt (min)	Area (%)
1	Geranyl propionate	Others (O)	$C_{13}H_{22}O_2$	9.166	1.28
2	D-Limonene	Monoterpene (M.O.T)	$C_{10}H_{16}$	10.705	1.32
3	Eucalyptol	M.O.T	$C_{10}H_{18}O$	10.790	**9.85**
4	Alpha-Ocimene	M.O.T	$C_{10}H_{16}$	10.866	3.48
5	Beta-Ocimene	M.O.T	$C_{10}H_{16}$	11.189	0.53
6	Sabinene hydrate	M.O.T	$C_{10}H_{18}O$	11.919	1.38
7	Linalool oxide	M.O.T	$C_{10}H_{18}O_2$	12.403	0.56
8	Linalool	M.O.T	$C_{10}H_{18}O$	12.883	**26.86**

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9	Allo-Ocimene	M.O.T	$C_{10}H_{16}$	13.643	0.99
10	2-Bornanone	M.O.T	$C_{10}H_{16}O$	14.229	4.03
11	Muurolol	Sesquiterpene (SE.T)	$C_{15}H_{26}O$	14.706	2.37
12	Borneol	M.O.T	$C_{10}H_{18}O$	15.002	**12.47**
13	Elemol	SE.T	$C_{15}H_{26}O$	15.230	**6.08**
14	Cryptone	O	$C_9H_{14}O$	15.372	0.94
15	Butanoic acid	M.O.T	$C_{10}H_{20}O_2$	15.465	1.06
16	Alpha-Terpineol	M.O.T	$C_{10}H_{18}O$	15.620	1.68
17	Bornyl acetate	O	$C_{12}H_{20}O_2$	16.598	0.83
18	Linalyl acetate	O	$C_{12}H_{20}O_2$	17.131	2.95
19	Nerol acetate	O	$C_{12}H_{20}O_2$	18.060	1.38
20	Carvacrol	M.O.T	$C_{10}H_{14}O$	18.483	0.79
21	Alpha-Santalene	SE.T	$C_{15}H_{24}$	21.765	0.53
22	Caryophyllene	SE.T	$C_{15}H_{24}$	21.828	2.43
23	Alpha-Bergamotene	SE.T	$C_{15}H_{24}$	22.114	0.76
24	Beta.-Farnesene	SE.T	$C_{15}H_{24}$	22.548	1.56
25	Alpha-Himachalene	SE.T	$C_{15}H_{24}$	22.611	0.85
26	Germacrene D	SE.T	$C_{15}H_{24}$	23.354	1.02
27	Decadienal	M.O.T	$C_{10}H_{16}O$	23.751	0.76
28	Beta-Himachalene	M.O.T	$C_{15}H_{24}$	23.839	1.32
29	Beta-Bisabolene	SE.T	$C_{15}H_{24}$	23.952	0.75
30	Alpha-Bisabolene	SE.T	$C_{15}H_{24}$	24.779	**5.30**
31	Caryophyllene oxide	SE.T	$C_{15}H_{24}O$	26.054	1.02
32	Bisabolol	SE.T	$C_{15}H_{26}O$	28.908	2.85

Chemical classes (Cl. CH)	
Monoterpene (M.O.T)	67.08
Sesquiterpene (SE.T)	25.52
Others (O)	7.38
Total identified (%)	**99.98**

C.Fo : Chemical formula ; Rt : Retention time ; Cl. CH : Chemical classes ; M.O.T : Monoterpene; SE.T : Sesquiterpene; O : Others; Cl.CH : Chemical class.

On the other hand, Satrani et al (2013) [43], reported an extraction yield of *C. atlantica* essential oil of around 2.78%, with a very high relative abundance of beta-himachalene (14.62%) and α-himachalene (5.72%). Their study also showed that fractional distillation yields four distinct fractions: the first rich in alcohols (26.40%) and ketones (32.74%), the second characterised by abundant ketones (38.73%), sesquiterpenes (25.79%) and terpene alcohols (15.01%), while the third and fourth fractions are dominated by ketones (42.16% and 44.38%) and sesquiterpenes (27.75% and 27.97%). Uwineza et al (2018) [44] also found a very high relative abundance of caryophyllene at 10.69% in their analyses. The differences observed in chemical composition can be explained by several factors. The plant's adaptation to abiotic conditions, such as the specific climate and geographical factors such as altitude and soil type, can direct biosynthesis

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towards the preferential production of certain metabolites [45]. Similarly, chemical composition can vary considerably depending on intrinsic factors such as sex, season, as well as ontogenetic and genetic variations [46–49]. This chemical diversity highlights the interest of *C. atlantica* essential oil for therapeutic, cosmetic, and aromatic uses, with potential applications that deserve further exploration.

3.2. Antioxidant activity of EO-CA

Essential oil are complex mixtures of bioactive molecules and various low-boiling organic compounds, which exhibit different antioxidant potencies in different biological systems. Therefore, in this work, we evaluated the antioxidant potential of *C. atlantica* essential oil using three complementary in vitro methods, namely, DPPH (2,2-diphenyl-1-picrylhydrazyl: radical scavenger), ferric reducing power (FRAP) and TAC method (total antioxidant capacity).

Assessment of antioxidant power using the DPPH method revealed a dose-dependent relationship for EO-CA. At a low concentration of 10 µg/mL, EO-CA showed a percentage inhibition of 37%, outperforming BHT and quercetin, which showed inhibitions of 25% and 23%, respectively (Figure 2). By increasing the concentration to 300 µg/mL, inhibition rose to 84% for EO-CA, while BHT and quercetin showed inhibitions of 86% and 68% respectively. These results suggest that EO-CA has significant antioxidant power, which increases as the concentration increases, rivalling reference antioxidants such as BHT and quercetin. This effectiveness could be attributed to the presence of bioactive compounds in EO-CA, which act by neutralising free radicals more effectively at higher concentrations.

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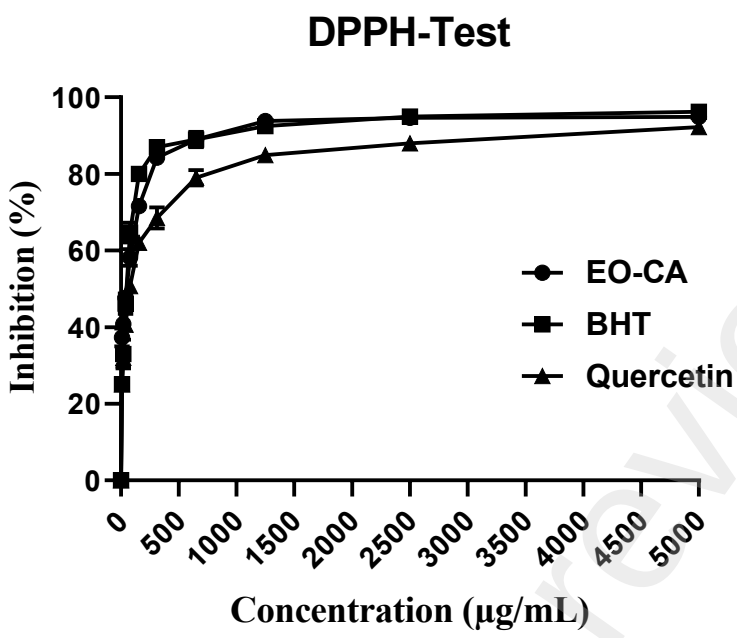

Figure 2. Antioxidant capacity of EO-CA, BHT and Quercetin by the DPPH method

To assess the antioxidant efficacy of EO-CA, BHT and quercetin, it is essential to determine the minimum inhibitory concentration (CI_{50}) required to reduce DPPH free radicals by 50%. The results, illustrated in Table 2, show that *C. atlantica* essential oil has significant antioxidant potential, with an IC_{50} of 48.52 ± 3.26 µg/mL. This result is comparatively close to that of BHT, a reference antioxidant, which has an IC_{50} of 39.61 ± 2.71 µg/mL. Furthermore, EO-CA shows greater antioxidant efficacy than quercetin, which has an IC_{50} of 64.39 ± 1.86 µg/mL. These data suggest that EO-CA could be a promising natural alternative for applications requiring antioxidant properties, rivalling even standards commonly used in the pharmaceutical industry.

The second test to evaluate the antioxidant power of EO-CA was carried out using the FRAP method. At a low concentration of 20 µg/mL, EO-CA showed an optical density (OD) of 150, while BHT and quercetin presented values of 130 and 128, respectively. At a higher concentration of 650 µg/mL, EO-CA showed an OD of 586, compared with 640 for BHT and 450 for quercetin (Figure 3). These results indicate that the antioxidant efficacy of EO-CA, like that of BHT and quercetin, is dose-dependent: the higher the concentration, the greater the improvement in antioxidant efficacy. EO-CA thus demonstrates considerable antioxidant potential, which increases with concentration. The results obtained by the FRAP method show that the essential oil of *C. atlantica* has a promising capacity to reduce ferrous ions, with an EC_{50} value of 415.62 ± 13.6 µg/mL (Table 2). In comparison, quercetin, with an EC_{50} value of

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345.86 ± 10.27 µg/mL, also confirms this ability to reduce ferrous ions. These results highlight the significant antioxidant potential of EO-CA, albeit slightly lower than that of quercetin, reinforcing the interest in using this essential oil for antioxidant applications.

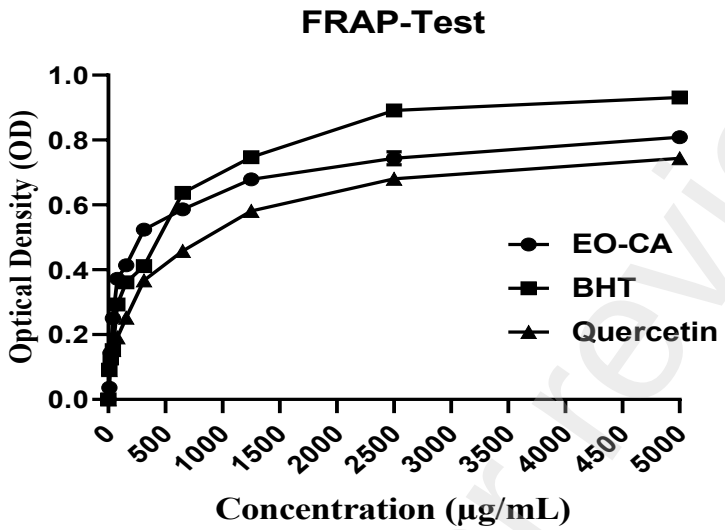

Figure 3. Antioxidant capacity of EO-CA, BHT and Quercetin by the FRAP method

The third test to evaluate the antioxidant power of EO-CA was carried out using the phosphomolybdate (TAC) method. At a concentration of 200 µg/mL, EO-CA demonstrated an antioxidant power of 334.0±25.45 µg AAE/mg, compared with 363.5±10.60 µg AAE/mg for BHT and 222.5±3.53 µg AAE/mg for quercetin (Figure 4). At a higher concentration of 500 µg/mL, the antioxidant efficacy of EO-CA, BHT and quercetin was measured at 640 µg EAA/mg, 725 µg EAA/mg, and 568.5 µg EAA/mg, respectively (Figure 4). In addition, the total antioxidant efficacy of EO-CA was 865±14.14 µg EAA/mg, while that of BHT was 929.0±40.30 µg EAA/mg and that of quercetin was 764.5±27.57 µg EAA/mg. These results confirm that *C. atlantica* essential oil has a significant antioxidant potential, although lower than that of BHT but higher than that of quercetin (Table 2).

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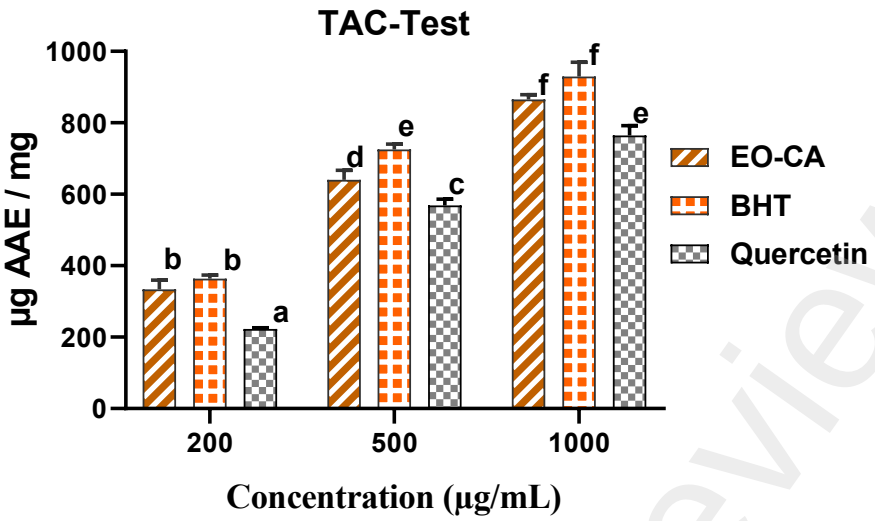

Figure 4. Antioxidant capacity of EO-CA, BHT, and quercetin assessed by the phosphomolybdate (TAC) method. Results are expressed as Mean ± SD, and values with the same letters (a, b, c, d, e, f) indicate no significant difference ($p<0.05$). EO-CA: Essential oil of *C. atlantica*.

Table 2. Antioxidant power of EO, BHT and quercetin by determining IC_{50}, EC_{50} and TAC

	DPPH (IC_{50} in µg/mL)	FRAP (EC_{50} in µg/mL)	TAC (µg AAE/mg)
EO-CA	48.52±3.26 [a]	415.62±13.60 [a]	865.0±14.14 [a]
BHT	39.61±2.71 [a]	472.43±15.48 [a]	929.50±40.30 [a]
Quercetin	64.39±1.86 [b]	345.86±10.27 [b]	764.50±27.57 [b]

Each column carries the same letter, so there is no significant difference ($p<0.05$).

Overall, the essential oil of *C. atlantica* analyzed showed remarkable antioxidant activity and higher inhibition, which is probably due to the effect and nature of the main chemical molecules with alcoholic function, such as linalool (26.86%), borneol (12.47%), 1,8 cineol (9.85%), alpha-bisabolene (5.30%), elemol (6.08%) and camphor (4.03%), several studies confirm that bioactive compounds with alcoholic function play an important role in their antioxidant power [50–52]. The results of our study agree with those obtained in the literature, for example for the DPPH method, the following IC_{50} values have been reported: 84 ± 63 µg/mL [53], 54 µg/mL [54], 53.24 ± 3.25 [55], 46.54 ± 3.64 µg/mL [56], 40 ± 110 µg/mL [57], 22.61 ± 1.08 [58], 19.0 ± 1, 1 µg/mL [59], 11.5 µg/mL [60], 6.25 µg/mL [61], 5.0 ± 0.4 µg/mL [62], 3.27 µg/mL [63], 2.0 ± 0.13 and 1.75 ± 0.69 µg/mL [64,65]. Furthermore, in a more recent study by Kačániová

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and al [66], *C. atlantica* essential oil showed the highest percentage of inhibition against DPPH radical. The undesirable side effects of synthetic antioxidants such as carcinogenicity and toxicity are immortal [67], which is why we recommend the use of *C. atlantica* essential oil from Morocco as an alternative naturally-derived antioxidant in medicine and nutrition. In some studies, some synthetic antioxidants were less effective than some plant-based essential oil [68]. In fact, essential oil show great promise in reducing oxidative reactions that occur during food handling, processing, and storage [69].

3.3. Antimicrobial power of EO-CA

The Figure 5 shows the antibacterial activity of EO-CA against three bacterial strains including *S. aureus*, *E. coli* and *K. pneumonia*. The results obtained show a high efficacy of EO-CA, particularly against *K. pneumonia*, with an inhibition diameter of 25.45 ± 1.15 mm. For ampicillin, the inhibition diameter did not exceed 09.58 ± 0.48 mm for this strain. It should also be noted that EO-CA inhibited the growth of *S. aureus* with a diameter of 22.07 ± 1.22 mm, this effect being greater than that obtained with ampicillin (10.28 ± 0.84 mm). Concerning *Escherichia coli*, the inhibition diameter was around 19.65 ± 1.24 mm, with EO-CA still in the majority compared with the marketed antibiotic (ampicillin).

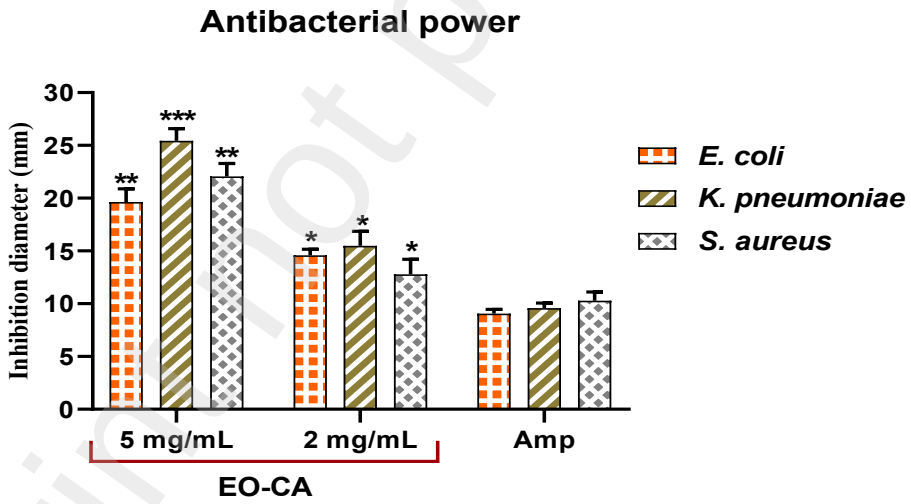

Figure 5. Evaluation of the antibacterial activity of EO-CA at various concentrations and the positive control (Amp) on solid medium using the disk diffusion method. Results are expressed as Mean ± SD, and values with the same letters (a, b, c, d, e, f) indicate no significant difference ($p<0.05$). Amp : ampicillin; EO-CA: Essential oil of *C. atlantica*.

The evaluation of the antibacterial activity of EO-CA revealed significant efficacy against three bacterial strains. The lowest MIC was observed for *K. pneumoniae* (95.68 ± 1.35 µg/mL), closely matching the effectiveness of ampicillin (91.82 ± 1.03 µg/mL). Against *S. aureus*

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(115.60 ± 0.84 µg/mL) and *E. coli* (138.40 ± 0.87 µg/mL), EO-CA demonstrated notable, albeit slightly lower, activity (Table 3). These effects are likely attributed to bioactive compounds such as linalool, which disrupt bacterial membranes and essential processes, potentially enhanced by the synergistic action of oxygenated monoterpenes and sesquiterpenes.

Evaluation of the antifungal activity of EO-CA against *C. albicans*, *S. cerevisiae* and *A. niger* using the disk diffusion method revealed strong antifungal activity. The results show that EO-CA has important activity against all three fungal strains, with an inhibition diameter of 23.83 ± 1.45 mm against *C. albicans*, an inhibition diameter of 20.65 ± 1.82 mm against *S. cerevisiae*, and an inhibition diameter of 19.69 ± 0.97 mm against *A. niger*. For the positive control (fluconazole), the inhibition diameter did not exceed 10.52 ± 0.78 mm, regardless of the fungal strain tested (Figure 6).

Table 3. Antimicrobial activity using the microdilution method

	Minimal inhibitory concentration (MIC in µg/mL)					
	Antibacterial activity			**Antifungal activity**		
	S. aureus	***K. pneumonia***	***E. coli***	***A. niger***	***C. albicans***	***S. cerevisiae***
EO-CA	115.60±0.84 ^{c}	95.68±1.35 ^{b}	138.40±0.87 ^{c}	147.09±2.49 ^{c}	115.69±2.08 ^{b}	85.81±1.38 ^{a}
AMP	69.30±0.93 ^{a}	91.82±1.03 ^{b}	127.80±1.61 ^{c}	-	-	-
Flu	-	-	-	67.81±1.41 ^{a}	73.59±0.91 ^{a}	66.92±1.07 ^{a}

Results are expressed as mean ± SD. Values with the same letters (a, b, c, d, e, f) within each activity indicate no significant difference ($p<0.05$). Flu: Fluconazole; Amp: Ampicillin; EO-CA: Essential oil of *Cedrus atlantica*.

EO-CA demonstrates promising antifungal activity, particularly against *S. cerevisiae* (85.81 ± 1.38 µg/mL), where its performance is comparable to fluconazole (66.92 ± 1.07 µg/mL). It also exhibits notable activity against *C. albicans* (115.69 ± 2.08 µg/mL), although slightly less effective than fluconazole (73.59 ± 0.91 µg/mL). Against *A. niger* (147.09 ± 2.49 µg/mL) (Table 3), the efficacy is lower but still significant. These activities are likely due to bioactive compounds like borneol and carvacrol, which disrupt fungal cell membranes and mitochondria, enhanced by the synergy between monoterpenes and sesquiterpenes.

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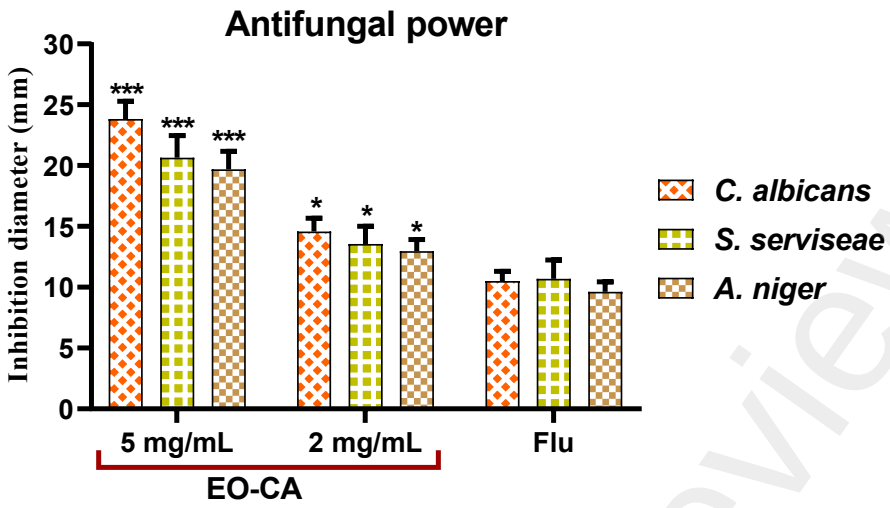

Figure 6. Evaluation of the antifungal activity of EO-CA at different concentrations and the positive control (Flu) on solid medium using the disk diffusion method. Results are expressed as Mean ± SD, and values with the same letters (a, b, c, d, e, f) indicate no significant difference ($p<0.05$). Flu: Fluconazole; EO-CA: Essential oil of *C. atlantica*.

In general, the antimicrobial effect of essential oil changes depending on the type of oil and the dilutions used. The entire chemical molecules are taken into account [50]. However, other research has demonstrated that when examined in isolation, EOs' antimicrobial activity outperforms that of the majority of other compounds [67]. The degree of synergistic effect that minority chemical molecules may have on the activity of essential oil is confirmed by the essential oils' dominance over the activity of a majority active ingredient [67].

Cedrus atlantica's antimicrobial effect can be attributed to its chemical molecules rich in oxygenated monoterpenes (linalool, borneol, eucalyptol and 2-bornanone), oxygenated sesquiterpenes (elemol) and hydrocarbon sesquiterpenes (alpha-bisabolene). These molecules have a very powerful antimicrobial effect; they exert their antimicrobial effect on pathogenic micro-organisms by disrupting the integrity of bacterial plasma membranes [70,71], resulting in altered cell permeability and inhibition of respiration [71].

Alpha-himachalene (0.85%) and beta-himachalene (1.32%) are two chemical molecules that characterize the essential oil of the Moroccan endemic plant, and are already known for their insecticidal activity [72,73]. The functional groups of certain compounds found in most plant materials, phenols, ketones, alcohol, terpenes and phenols, are associated for their antimicrobial characteristics [74]. In some studies, authors have suggested the resistance of *S. aureus* to other strains of *C. atlantica* essential oil [75]. It has been demonstrated by others that strains respond differently based on the cedar oil's composition [75]. There is evidence that minor components

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play an essential role in antibacterial activity, perhaps by producing a synergistic effect between other components [76].

3.4. Molecular Docking

Molecular docking was carried out to theoretically evaluate the antioxidant and antimicrobial potential of *C. atlantica* (L.) essential oil (EO) components. The choice of target proteins was based on their key role in the regulation of oxidative stress and microbial survival mechanisms. Inhibition of NADPH oxidase, essential for the production of reactive oxygen species (ROS), is a crucial step in maintaining cellular redox balance and reinforcing antioxidant defenses. Among the ligands tested, sabinene hydrate proved to be the most potent inhibitor of NADPH oxidase, with a glide score of -5.817 kcal/mol, followed by cryptone (-5.656 kcal/mol) and carvacrol (-5.548 kcal/mol) (Table 4).

Table 4. Docking results in ligands in different receptors

	glide gscore (Kcal/mol)				
	2CDU	1FJ4	3Q8U	5I77	5FSA
2-Bornanone	-3.759	-5.95	-5.156	-4.563	-5.48
Allo-Ocimene		-4.344	-3.23	-2.661	-3.914
Alpha-Bergamotene	-3.026	-4.878	-3.392	-3.201	-5.637
Alpha-Bisabolene	-3.375	-6.395	-4.139	-3.476	-6.078
Alpha-Himachalene	-5.196	-4.002	-3.914		-7.034
Alpha-Ocimene	-1.156	-3.146	-2.015	-1.588	-2.349
Alpha-Santalene		-4.929	-3.741	-3.25	-6.055
Alpha-Terpineol	-4.055	-6.102	-4.874	-4.192	-5.921
Beta-Bisabolene	1.295	-5.411	-4.056	-3.379	-4.896
beta-Farnesene	-3.82	-1.405	0.216	1.015	-1.363
Beta-Himachalene		-4.016	-3.112		-6.854
Beta-Ocimene	-2.359	-3.769	-2.106	-2.245	-3.337
Bisabolol	-3.389	-6.064	-3.632	-3.489	-4.706
Borneol	-3.406	-6.381	-4.613	-5.41	-6.303
Bornyl acetate	-3.609	-6.495	-4.651	-4.337	-5.72
Bornyl acetate	-3.399	-5.917	-4.5	-3.832	-5.593
Butanoic acid	-5.313	-4.846	-7.903	-4.203	-4.312

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Carvacrol	-5.548	-6.516	-4.905	-5.321	-6.791
Caryophyllene	-3.94	-5.056	-3.298		-7.025
Cryptone	-5.656	-6.792	-5.035	-5.107	-5.441
Decadienal	-2.559	-4.247	-3.362	-2.141	-2.746
D-Limonene	-3.395	-5.08	-4.015	-3.938	-4.219
Elemol	-3.402	-4.577	-4.348	-3.309	-6.188
Eucalyptol	-3.312	-5.703	-3.275	-4.543	-4.739
Geranyl propionate	0.425	-1.913	-2.312	-0.75	-2.4
Germacrene D	-3.08	-5.993	-3.202		-6.825
Linalool	-2.325	-3.99	-3.158	-2.721	-3.673
Linalool oxide	-3.544	-5.039	-4.381	-4.414	-6.026
Linalyl acetate	-2.731	-5.067	-3.604	-2.863	-4.636
Muurolol	-2.942	-5.976	-4.503		-6.933
Nerol acetate	-3.032	-5.364	-4.419	-2.426	-4.48
Sabinene hydrate	-5.817	-6.564	-5.029	-5.481	-6.259

However, interaction analysis showed that sabinene hydrate, despite its high score, did not establish specific bonds with active site residues (Figures 7A and 8A), underlining the need for cautious interpretation of docking results. With regard to antimicrobial activity, cryptone, sabinene hydrate, and carvacrol showed high affinities for *E. coli* beta-ketoacyl-[acyl carrier protein] synthase (glide scores of -6.792, -6.564, and -6.516 kcal/mol, respectively). Cryptone interacts with residues THR 300 and THR 302 via hydrogen bonds (Figures 7B and 8B). For *S. aureus*, butanoic acid displayed the highest affinity (-7.903 kcal/mol), forming a hydrogen bond with residue HIE 52 and a salt bridge with residue MG 159 (Figures 7C and 8C).

In terms of antifungal activity, alpha-himachalene (-7.034 kcal/mol), caryophyllene (-7.025 kcal/mol), and muurolol (-6.933 kcal/mol) showed the highest glide scores against *C. albicans*. However, alpha-himachalene, despite its high score, failed to form specific bonds in the active site, highlighting the importance of other factors such as steric effects or ligand abundance in the observed activity (Figures 7D and 8D). Against *A. niger*, sabinene hydrate formed two hydrogen bonds with residues SER 196 and TRP 201, confirming its antifungal potential (Figures 7D and 8D)

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GC-MS analysis of *Cedrus atlantica* (L.) essential oil revealed a diversity of chemical compounds, primarily monoterpenes (67.08%) and sesquiterpenes (25.52%), along with traces of other compounds (7.38%). Among the most abundant compounds, linalool (26.86%), borneol (12.47%), and eucalyptol (9.85%) were identified as major constituents, together accounting for over 50% of the essential oil [77,78].

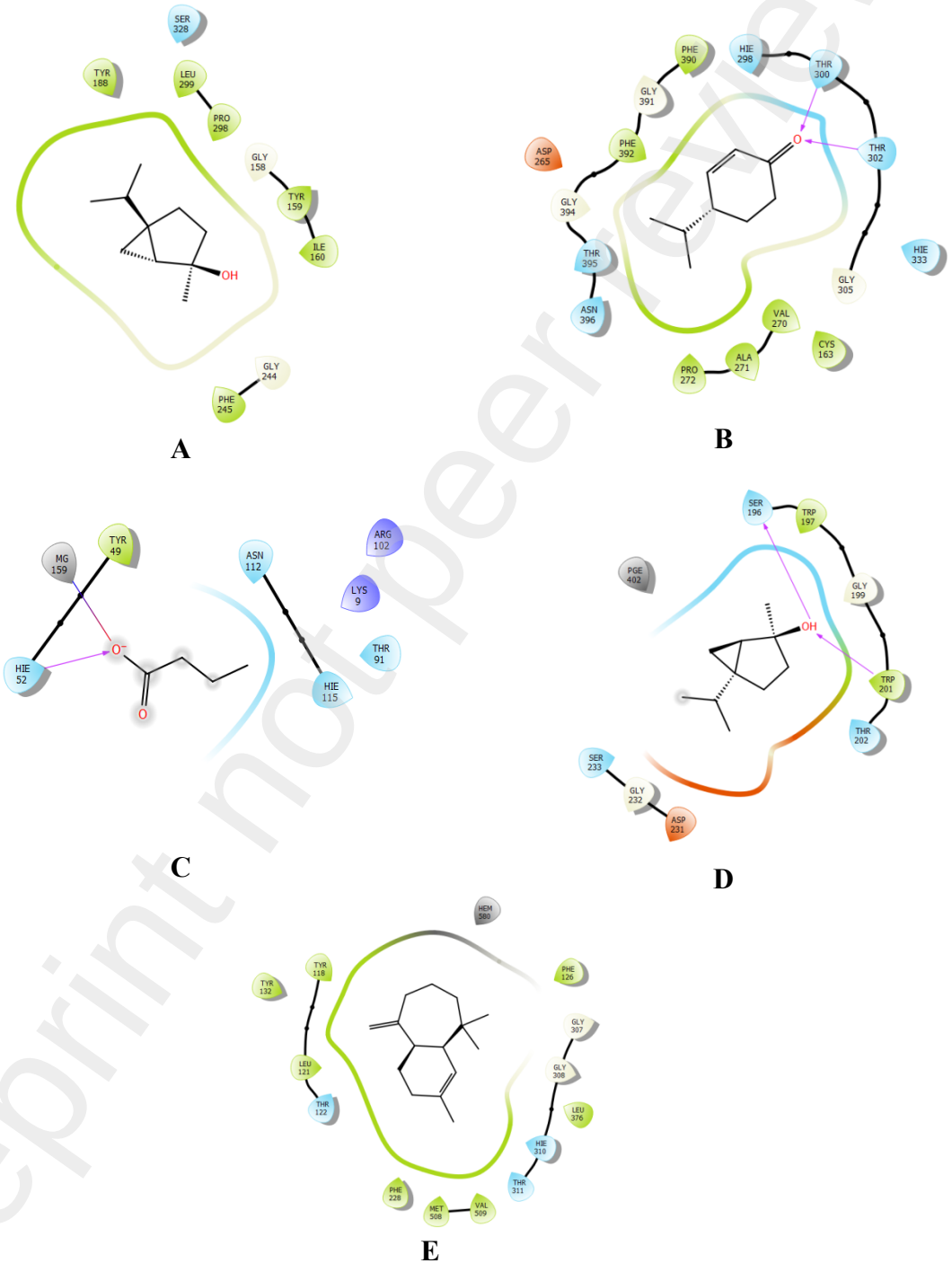

Figure 7: The 2D viewer of ligands interactions with the active site. (A): sabinene hydrate interactions with the active site of NADPH oxidase. (B): cryptone interactions with the

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energetic site of beta-ketoacyl-[acyl carrier protein] synthase from *E. coli*. (C): butanoic acid interactions with the active site of *S. aureus* nucleoside diphosphate kinase. (D): alpha-himachaleneinteractions with the active site of sterol 14-alpha demethylase (CYP51) from a pathogenic yeast *C. albicans*. (E): sabinene hydrate with the energetic site of a beta-1,4-endoglucanase from *A. niger*.

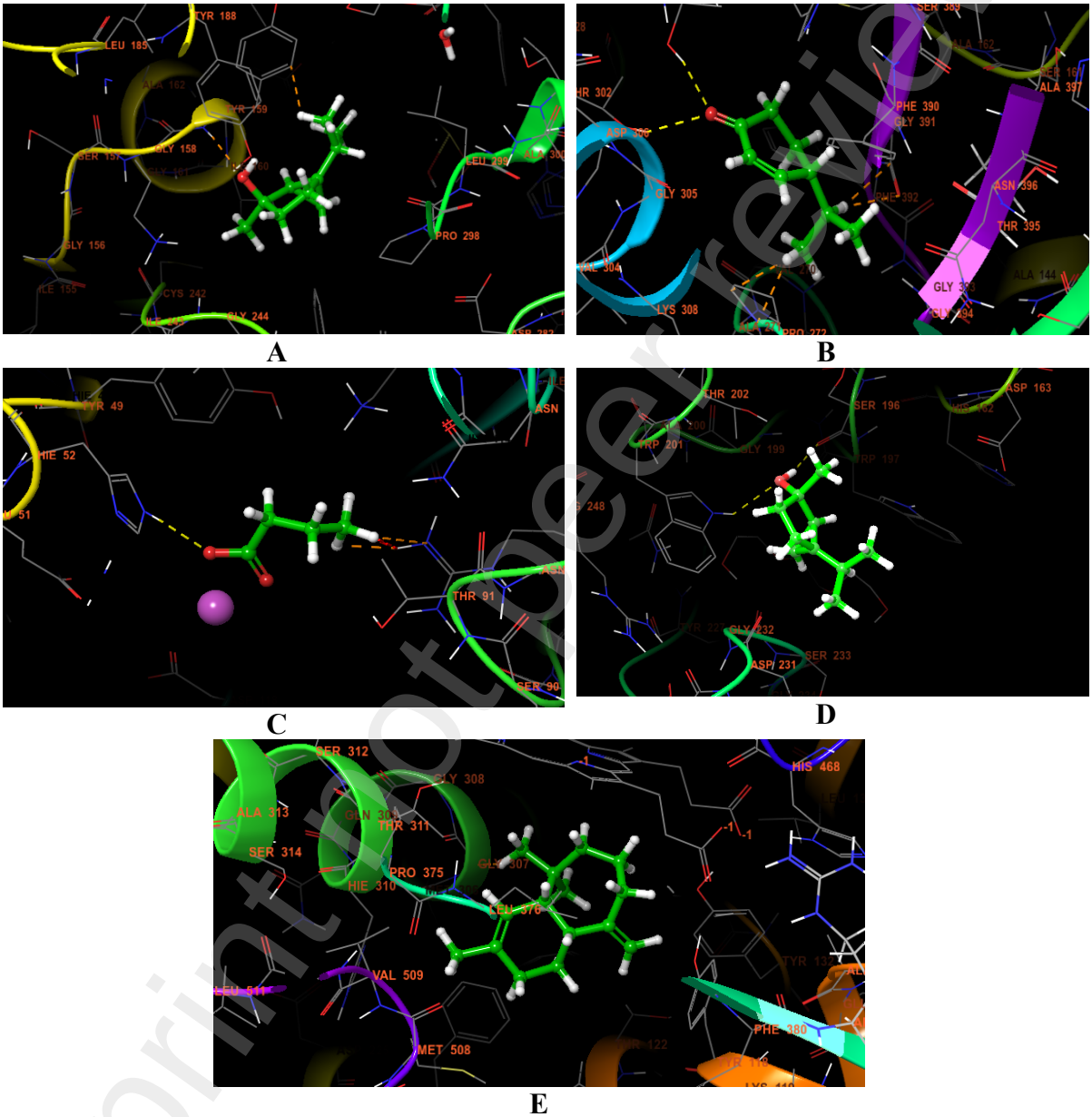

Figure 8: The 3D viewer of ligands interactions with the active site. (A): sabinene hydrate interactions with the active site of NADPH oxidase. (B): cryptone interactions with the energetic site of beta-ketoacyl-[acyl carrier protein] synthase from *E coli*. (C): butanoic acid interactions with the active site of *S. aureus* nucleoside diphosphate kinase. (D): alpha-himachaleneinteractions with the active site of sterol 14-alpha demethylase (CYP51) from a

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pathogenic yeast *C. albicans*. (E): sabinene hydrate with the energetic site of a beta-1,4-endoglucanase from *A. niger*.

Linalool, as the main compound, is well-known for its antioxidant and antimicrobial properties. Its structure, which includes a hydroxyl group and a double bond, may explain its biological activity through interactions with the active sites of target receptors [78,79]. Borneol, present at 12.47%, also demonstrated significant affinity for several receptors in docking analysis, further reinforcing its potential role in the essential oil's biological activities. Although borneol exhibited a lower docking score compared to other compounds such as sabinene hydrate, its relatively high concentration in the essential oil (12.47%) suggests that it could exert a synergistic effect with other molecules [80].

The interaction between the chemical structure of the compounds and their biological activity can be understood through the structure-activity relationship (SAR). Monoterpenes, such as linalool and sabinene hydrate, are frequently associated with antioxidant and antimicrobial properties due to their relatively simple structures and the presence of reactive functional groups [80,81]. Sesquiterpenes, such as caryophyllene and muurolol, have also demonstrated strong activity, particularly against *C. albicans*, and may be responsible for the antifungal effects observed. This analysis highlights the importance of integrating GC-MS data with docking results to gain a deeper understanding of the biological activity of essential oils. The findings underscore that even compounds with lower binding affinities can significantly influence the overall biological activity due to their abundance in the essential oil [77].

4. Conclusion

Phytochemical characterisation by GC-MS of the essential oil extracted from *Cedrus atlantica* revealed a composition rich in bioactive compounds (32 compounds), underlining the therapeutic potential of this medicinal plant. Various *in vitro* evaluations, carried out using tried and tested methods, confirmed the antioxidant efficacy of these essential oil. Their ability to neutralise free radicals, demonstrated by tests such as DPPH (IC_{50} of 48.52 ± 3.26 µg/mL), FRAP (EC_{50} of 415.62 ± 13.60 µg/mL) and TAC (865.0 ± 14.14 µg AAE/mg), is particularly promising and suggests that *C. atlantica* could play a crucial role in preventing diseases linked to oxidative stress. In parallel, assessment of the antimicrobial activity revealed interesting potential against various bacterial strains (inhibition diameters ranging from 19.65 mm to 25.45 mm) and fungal strains (inhibition diameters ranging from 19.69 mm to 23.83 mm), reinforcing

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the interest in using these essential oil as natural alternatives to synthetic antimicrobials. This antibacterial and antifungal activity, combined with antioxidant efficacy, positions *C. atlantica* as a potential source of multifunctional therapeutic compounds. These results not only support the traditional use of this species in folk medicine, but also pave the way for broader applications in the pharmaceutical and cosmetics fields. To maximise the benefits of *C. atlantica*, further studies are required, particularly into the mechanisms of action of its active compounds, as well as the optimisation of extraction methods to obtain even higher yields of essential oil.

Conflicts of Interest: The authors declare no conflicts of interest.

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